

Docket 85677LMB  
Customer No. 01333

**IN THE UNITED STATES PATENT AND TRADEMARK OFFICE**  
**BEFORE THE BOARD OF PATENT APPEALS AND INTERFERENCES**

In re Application of

Kurt M. Schroeder, et al

COLORABLE POLYMERIC  
PARTICLES WITH BIOLOGICAL  
PROBES

Serial No. 10/625,637

Filed 23 July 2003

Group Art Unit: 1743

Examiner: Paul S. Hyun

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Alexandria, VA. 22313-1450

Sir:

**APPEAL BRIEF PURSUANT TO 37 C.F.R. 41.37 and 35 U.S.C. 134**

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### **APPELLANT'S BRIEF ON APPEAL**

Appellants hereby appeal to the Board of Patent Appeals and Interferences from the Examiner's Final Rejection of claims 24-39 which was contained in the Office Action mailed 11/13/2006.

A timely Notice of Appeal was filed 2/13/2007.

### **Real Party In Interest**

As indicated above in the caption of the Brief, the Eastman Kodak Company is the real party in interest.

### **Related Appeals And Interferences**

No appeals or interferences are known which will directly affect or be directly affected by or have bearing on the Board's decision in the pending appeal.

### **Status Of The Claims**

Claims 1-40 are pending in the application.

Claims 1-23 and 40 stand withdrawn from consideration as directed to a non-elected invention, pursuant to a restriction requirement made by the Examiner in an Office Action dated 11/15/2005, and the Applicant's election made in the Response dated 2/15/2006.

Claims 24-39 are being appealed.

Appendix I provides a clean, double spaced copy of the claims on appeal.

### **Status Of Amendments**

An Amendment After Final, including only remarks, was filed on January 16, 2007, subsequent to the Final Rejection. An Advisory Action dated February 9, 2007 was then received indicating that the Examiner reconsidered, but did not find that the remarks were sufficiently persuasive to place the Application in condition for allowance.

### **Summary of Claimed Subject Matter**

The invention relates to biological microarray technology (page 1, line 14). In particular, the invention relates to a polymeric particle, also known as a microsphere, for use in a microarray (page 3, line 10-12). A colorable particle can

be prepared for use as bindable substances in biological applications by solvating a polymeric microsphere particle with a photographic coupler and a high boiling organic solvent (page 2, lines 14-17). The high boiling organic solvent does not substantially evaporate during particle formation (page 2, lines 17-19). The photographic coupler is capable of forming color after a suitable chemical development (page 4, lines 28-30).

Independent claim 24 recites a polymeric particle for use in a microarray (page 2, lines 30-31), the microarray having a polymeric particle with at least one functionally active group that can interact with a biological probe (page 3, lines 12-13), at least one photographic coupler (page 3, lines 22-25), and a high boiling solvent (page 3, lines 22-25). The polymeric particle is loaded with at least one photographic coupler and a high boiling solvent (page 13, lines 6-10).

### **Grounds of Rejection to be Reviewed on Appeal**

The following issue is presented for review by the Board of Patent Appeals and Interferences:

1. Whether claims 24-39 are unpatentable under 35 U.S.C. § 103(a) over Rembaum et al. (U.S. 4,929,400) in view of Mihara et al. (U.S. 4,331,444) and de Jaeger et al. (U.S. 4,837,168).

### **Arguments**

#### **Rejection of claims 24-39 under 35 U.S.C. § 103(a) over Rembaum et al. in view of Mihara et al. and de Jaeger et al.:**

In the Final Office Action dated November 13, 2006 claims 24-39 stand rejected under 35 U.S.C. § 103(a) as being unpatentable over Rembaum et al. (U.S. 4,929,400) in view of Mihara et al. (U.S. 4,331,444) and de Jaeger et al. (U.S. 4,837,168).

The Examiner indicates that Rembaum et al. discloses polymeric microspheres adapted to be used for immunoassays and a method for producing them, the microspheres are acrylic and can range from 1000 Angstroms to 100 microns in size, each microsphere comprises functional groups (i.e. aldehyde) capable of binding proteins and a dye for visually detecting the microspheres. The Examiner further indicates that the reference to Rembaum et al. does not disclose

that the dye comprises a photographic couple, but that de Jaeger et al. discloses latex label adapted to be used for immunoassays in which the latex particles are coupled to dye-forming couplers that can be developed to form cyan, magenta or yellow dyes, the dyes are used to visually detect the occurrence of a reaction of interest, and the reference discloses that phenol or a naphthol type compounds produce cyan dyes, pyrazolone type compounds form magenta dyes and open chain ketomethylene type compounds form yellow dyes. The Examiner further indicates that Mihara et al. disclose a method for immunoassay using a phenol or a naphthol coupler, a pyrazolone coupler, and an open chain ketomethylene coupler that are developed by oxidizing developing agents to form cyan, magenta or yellow dyes, respectively and that the couplers are dissolved in high boiling solvents, making it obvious to one of ordinary skill in the art to dye the microspheres disclosed by Rembaum et al. with the dye-forming couplers dissolved in high boiling solvents disclosed by Mihara et al. and de Jaeger et al. since the 3 dye colors provide versatility and diversity in detection.

This rejection is respectfully urged as in error and reversal is requested as the references fail to teach or suggest microspheres which are imbibed with a photographic coupler and a high boiling solvent.

**The References fail to disclose all of the presently claimed limitations:**

Rembaum discloses a process for the production of polymeric particles and, more particularly, evenly sized, magnetic or non-magnetic, microspheres by the polymerization of falling or suspended uniformly-sized and shaped droplets in a containerless environment. The polymeric microspheres with very precise size and a wide variation in monomer type and properties are produced by deploying a precisely formed liquid monomer droplet, suitably an acrylic compound such as hydroxyethyl methacrylate into a containerless environment. The droplet which assumes a spheroid shape is subjected to polymerizing radiation such as ultraviolet or gamma radiation as it travels through the environment. Rembaum fails to disclose a microsphere loaded with both a photographic coupler and a high boiling organic solvent.

Mihara et al. discloses a method for photochemically analyzing, in a quantitative manner, trace components utilizing immune reaction by marking or labeling an antigen or antibody with a marker. An immune reaction is caused using an antigen or antibody marked with a fogging agent for silver halide, the labeled antigen or antibody is separated from the labeled antigen-antibody reaction product, the silver halide is developed in the presence of either one of the labeled antigen or antibody and the labeled antigen-antibody reaction product, and the density obtained is measured. The method is comparable to radioimmunoassay in having high reproductibility and sufficient sensitivity but does not involve any risk due to radiation. In Mihara, the coupler is dissolved into a high boiling organic solvent and dispersed in a gelatin binder along with silver halide particles, to provide a silver halide particle tagged with a fogging agent/biological probe complex and coupler, all dispersed in a gelatin binder. The coupler is not loaded in a microsphere. In Mihara, the amount of coupler that gets developed into dye depends on the amount of silver halide particles that are fogged by the complex of the antigen and fogging agent that is attached to the surface of the silver halide particles. The color forms as a dye cloud around the exterior of the silver halide particles as development occurs. Mihara fails to disclose microspheres, including a microsphere loaded with both a coupler and a high boiling solvent.

DeJaeger et al. relates to a method for the detection of specific binding agents and their corresponding bindable substances by employing a label which is a latex particle which can be visually detected. DeJaeger fails to disclose a microsphere loaded with both a coupler and a high boiling solvent.

The present invention relates to a polymeric particle for use in a microarray comprising polymeric particle, loaded with at least one photographic coupler and high boiling solvent, and having at least one functionally active group that can interact with a biological probe. In the case of the polymer particles of the present invention, the developer penetrates the microsphere, with the aid of the high boiling solvent, to reach the loaded coupler and the developed coupler, still loaded in the microsphere, produces a colored microsphere. These particles are readily observable in a microscope after they develop color.

To establish a *prima facia* case of obviousness requires, first, there must be some suggestion or motivation, either in the references themselves, or in the knowledge generally available to one of ordinary skill in the art, to modify the reference or to combine reference teachings. Second, there must be a reasonable expectation of success. Finally, the prior art references (or references when combines) must teach or suggest all the claim limitations. The level of skill in the art cannot be relied upon to provide the suggestion to combine references. *In re Vaeck*, 947 F.2d 488, 20 USPQ2d 1438 (Fed. Cir. 1991). The teaching or suggestion to make the claimed combination and the reasonable expectation of success must both be found in the prior art, not in the applicant's disclosure. *In re Rouffet*, 149 F.3d 1350, 1357, 47 USPQ2d 1453, 1457-58 (Fed. Cir. 1998).

The present invention relates to a microsphere loaded with both a photographic coupler and a high boiling solvent. Rembaum et al. discloses polymer microspheres, but fails to disclose microsphere which are loaded with photographic coupler and high boiling solvent as claimed by the instant invention. De Jaeger et al. teaches microspheres containing photographic coupler, but fails to teach microspheres containing both a high boiling solvent and a photographic coupler as claimed by the instant invention. In fact, de Jaeger et al. teaches the use of low boiling solvent that can be easily removed from the aqueous reaction medium by distillation during or after the polymerization. Mihara et al. teaches the use of photographic couplers in silver-halide emulsion layers and the use of both high and low boiling solvents, to introduce the couplers into the silver-halide emulsion layer. However, Mihara et al. fails to mention the introduction of photographic coupler, high boiling solvents, or both photographic coupler and high boiling solvent into a microsphere as claimed by the instant invention. As disclosed in U.S. Pat. No. 5,585,230 it is desirable to remove solvent after preparing the dispersions for silver halide emulsions prior to coating. As shown on Col. 7, line 59 through Col. 8, line 67, the solvent is generally removed by evaporation, noodle washing, or membrane dialysis. Therefore, it would be desirable to remove the solvent as taught by Mihara et al. prior to coating onto a substrate. Therefore, Mihara et al. fails to teach or suggest a polymeric particle loaded with a high boiling solvent as claimed by the instant invention.

None of the references discloses a polymeric particle containing a photographic coupler and a high boiling solvent. Particularly, none of the references teach a microsphere loaded with a high boiling solvent. At best, a combination of the references would produce a microsphere containing coupler, which is soluble in high and low boiling organic solvents.

**The References Lack Likelihood of Success and Motivation for Combination:**

In the Final Office Action dated November 13, 2006 the Examiner asserts that there is motivation for combining the three references. The Examiner states that Rembaum et al. discloses polymeric microspheres comprising a dye for visually detecting the microspheres and that the particles disclosed by Rembaum et al. and the claimed invention are distinct in two ways: 1) the dye disclosed by Rembaum et al. differs from the dye of the claimed invention; and 2) the microsphere disclosed by Rembaum et al. lacks a high-boiling solvent.

The Examiner indicates that de Jaeger et al. discloses latex particles adapted to be used for immunoassays, and that the latex particles are coupled to dye-forming couplers that can be developed to form cyan, magenta or yellow dyes. The Examiner asserts that the reference discloses that phenol or a naphthol type compounds produce cyan dyes, pyrazolone type compounds form magenta dyes and open chain ketomethylene type compounds form yellow dyes. The Examiner states that in light of the disclosure of de Jaeger et al., it would have been obvious to substitute the dye disclosed by Rembaum et al. with the dye disclosed by de Jaeger et al. because the dye combination disclosed by de Jaeger et al. provides versatility and diversity in detection.

The Examiner further indicates that Mihara et al. discloses a method for immunoassay using a phenol or a naphthol coupler, a pyrazolone coupler, and an open chain ketomethylene coupler. The Examiner states the dyes disclosed by Mihara et al. are identical to the dyes disclosed by de Jaeger et al. Mihara et al. disclose that the couplers can be dissolved in high boiling solvents before the solution is applied to the target substrate or support. The Examiner states that in light of the disclosure of Mihara et al., it would have been obvious to one of ordinary skill in the art to dissolve the dyes disclosed by de Jaeger et al. in dibutyl

phthalate and then apply the solution to the microspheres disclosed by Rembaum et al. to simplify the application process of the dyes to the microspheres.

The Examiner further asserts that there is also likelihood of success in combining the references. The Examiner states that the only modification made to the microspheres disclosed by Rembaum et al. is the dyes coupled to the microspheres. The Examiner asserts that one of ordinary skill in the art would have recognized a way to couple the dyes disclosed by de Jaeger et al. and Mihara et al. to the microspheres disclosed by Rembaum et al., especially since the microspheres disclosed by Rembaum et al. comprise functional groups for binding complimentary functional groups.

This assertion is urged as in error as the references fail to mention the presence of high boiling solvent in a polymeric particle and further lack a likelihood of success.

Neither de Jaeger et al. nor Rembaum et al. disclose the presence of solvent, especially a high boiling solvent, in a microparticle as claimed by the instating invention. Mihara et al. does not provide any motivation for loading high boiling solvent into polymeric particles, and fails to disclose polymeric particles in their entirety. MPEP 2143.01 III indicates that the “fact that references can be combined or modified is not sufficient to establish *prima facia* obviousness.” “Although a prior art device “may be capable of being modified to run the way the apparatus is claimed, there must be a suggestion or motivation in the reference to do so.” 916 F.2d at 682, 16 USPQ2d at 1432.). The references fail to teach or suggest the problem solved by the instant invention. The addition of high boiling solvent loaded into a microsphere enhances color development. As discussed above, it is desirable to remove solvent prior to forming a silver halide element as taught by Mihara et al. There is no motivation provided by the references to load high boiling solvent into a microsphere.

Furthermore, there is no likelihood of success in combining the references. The Examiner indicates that it would have been obvious to one of ordinary skill in the art to dye the microspheres disclosed by Rembaum et al. with the dye-forming couplers dissolved in high boiling solvents disclosed by Mihara et al. and de Jaeger et al. since the 3 dye colors provide versatility and diversity in detection.

However, none of the references teach a microsphere containing, specifically, high boiling solvent, and therefore produce no likelihood of success in producing a microsphere containing high boiling solvent. The present specification indicates, "Particles in the sub-micronic range (nominally less than 100 nanometers) are difficult to detect by optical means. In addition, a polymeric bead solvated with a color forming moiety is difficult to develop into color using chemical means."

The examples of the present specification indicate that the presence of the high boiling solvent in the microsphere enhances the intensity of the developed color by maximizing developed dye density (pg. 13, lines 21-25), resulting in enhanced penetration of developer into the microsphere, making the small particles easier to detect and individually identify than microspheres containing coupler alone. See Table I, pg. 24. It is the solubility of the developer in the high boiling solvent that results in enhanced color development, not the solubility of the loaded coupler in the high boiling solvent. The cited prior art is silent with regard to the solubility of developer in high boiling solvent, resulting in enhanced color development of coupler loaded in a microsphere in which high boiling solvent is also loaded. The presence of the high boiling solvent in the microsphere results in the improved penetration of developer into the microsphere to reach the dye. The references are silent relating to the penetration of the high boiling solvent into the microsphere. The references are also silent regarding the fact that the high boiling solvent is still present when the developer is added, which enhances color development. The references provide no likelihood of success relating to the high boiling solvent loaded in the microspheres, which is key to the improved color development.

Additionally, the instant invention has surprising results. Table I, pg. 24 indicates that the use of high boiling solvent provides enhanced color formation - as compared to the use of coupler in microspheres alone. Since the undeveloped coupler is loaded in the microsphere, developer must reach the coupler to produce developed coupler, i.e., color. The presence of high boiling solvent in the microsphere enhances developer penetration, resulting in increased development of the loaded coupler, and enhanced color. The presence of the high boiling

solvent in the microsphere, which enhances the penetration of the developer into the microsphere to increase the amount of dye developed, and, hence enhancing the color, is a surprising result, based on the teachings found in the prior art.

**Examiner's response to Applicant's Arguments:**

In the Advisory Action dated February 9, 2007 the Examiner states that Applicant's arguments are not persuasive. The Examiner indicates that Mihara et al. discloses a method for applying the claimed dyes onto a substrate. The method comprises the step of dissolving the dyes in a high-boiling point organic solvent prior to applying the solution to a substrate. The Examiner states that from the disclosure, it appears that the purpose of the organic solvent is to dissolve the hydrophobic dye so that the dye can be applied to a substrate. The Examiner further states that the substrate onto which the dye solution is applied does not appear to be significant to the reason for using the solvent, and therefore, based on the teachings of Mihara et al., it would have been obvious to one of ordinary skill in the art to dissolve the dyes in a high-boiling solvent prior to applying the solution to any substrate, including microspheres. The Examiner asserts that because the dyes are dissolved in the solvent, it naturally flows that the solvent would be loaded into the microspheres along with the dyes.

As previously discussed, none of the references teach, suggest or disclose a polymeric particle containing a photographic coupler, wherein the microsphere also contains a high boiling solvent. As a result, the references fail to teach all the claimed limitations.

As discussed above, the references lack motivation for combination as the references fail to mention the presence of high boiling solvent in a polymeric particle. Also as discussed above, the references fail to produce a likelihood of success in producing a microsphere containing high boiling solvent.

**Summary**

Neither de Jaeger et al. nor Rembaum et al. disclose a high boiling solvent, much less a polymeric particle loaded with high boiling solvent as taught by the

instant invention. Furthermore, neither reference teaches or suggests solving the problem solved by the instant invention by including high boiling solvent in a polymeric particle to improve color development.

Mihara et al. fails to mention the introduction of high boiling solvents into a polymeric particle as claimed by the instant invention. Mihara et al. teaches the use of high boiling solvents to introduce couplers into a silver halide emulsion. However, solvents are generally removed in the process forming a multilayer coating for photographic elements. Mihara et al. does not disclose that high boiling solvent is present in the immunoassay. To the contrary, traditional methods silver halide coating methods suggest the removal of solvent.

Additionally, Mihara et al. fails to disclose polymeric particles and instead relates to a coating method. The purpose of solvent for coating methods is to introduce couplers into a silver halide emulsion. The instant invention enhances color development of coupler loaded in a microsphere by utilizing high boiling solvent, which is also loaded. The presence of the high boiling solvent in the microsphere results in the improved penetration of developer into the microsphere to reach the dye.

The references lack motivation for combination and fail to demonstrate any likelihood of success. The references do not provide any motivation for loading high boiling solvent into polymeric particles. No reference reveals the addition of high boiling solvent loaded into a microsphere enhances color development. The references do not teach a microsphere containing high boiling solvent, and therefore produce no likelihood of success in producing a microsphere containing high boiling solvent. The present specification indicates that polymeric particles are difficult to detect by optical means, and that a polymeric bead solvated with a color forming moiety is difficult to develop into color using chemical means. The references fail to disclose any solution or motivation to solve this problem.

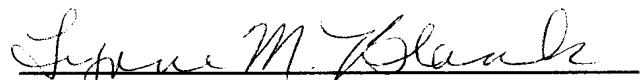
To establish a *prima facia* case of obviousness more than hindsight analysis is required as a basis to reject the claims. In the present case the Office has failed to provide more than a hindsight basis for the rejection of the claims. Furthermore, applying a hindsight reconstruction of the references cited, the

references lack likelihood of success at arriving at the instant invention as claimed and fail to teach an operable invention. The failure to provide an adequate basis for the rejection should be recognized and the claims should, by regular aspects of the law and United States Patent and Trademark Office rules, be issued as letters patent to the Applicants.

### **Conclusion**

For the above reasons, Appellants respectfully request that the Board of Patent Appeals and Interferences reverse the rejection by the Examiner and mandate the allowance of Claims 24-39.

Respectfully submitted,



Attorney for Appellants  
Registration No. 42,334

Lynne M. Blank/ct  
Telephone: 585-477-7418  
Facsimile: 585-477-1148  
Enclosures

If the Examiner is unable to reach the Applicant(s) Attorney at the telephone number provided, the Examiner is requested to communicate with Eastman Kodak Company Patent Operations at (585) 477-4656.

## **Appendix I - Claims on Appeal**

24. A polymeric particle for use in a microarray comprising a loaded polymeric particle having at least one functionally active group that can interact with a biological probe;

at least one photographic coupler; and

a high boiling solvent, wherein said polymeric particle is loaded with said at least one photographic coupler and said high boiling solvent.

25. The polymeric particle of claim 24 with a biological probe covalently or noncovalently attached.

26. The polymeric particle of claim 24, formed from styrenic polymers, acrylic polymers, or from a polyester-addition polymer hybrid.

27. The polymeric particle of claim 24 wherein the loaded polymeric particle has a mean diameter of 1 to 50 microns.

28. The polymeric particle of claim 24 wherein the loaded polymeric particle has a mean diameter of 3 to 30 microns.

29. The polymeric particle of claim 24 wherein the loaded polymeric particle has a mean diameter of 5 to 20 microns.

30. The polymeric particle of claim 24 wherein the functionally active groups on the surface of the loaded polymeric particle can interact with biological probes.

31. The polymeric particle of claim 24 wherein the functionally active group on the surface of the loaded polymeric particle is carboxyl, amino, hydroxyl, hydrazide, amide, chloromethyl, epoxy, or aldehyde.

32. The polymeric particle of claim 24 wherein the biological probes are covalently or noncovalently attached to the surface of the loaded polymeric particle.

33. The polymeric particle of claim 24 wherein the coupler in the loaded polymeric particle can be developed to form a detectable color.

34. The polymeric particle of claim 33 wherein the photographic coupler is developed by interacting with oxidizing color developing agents to form cyan, magenta or yellow dyes.

35. The polymeric particle of claim 24 wherein the photographic coupler is a phenol or a naphthol that forms cyan dyes.

36. The polymeric particle of claim 24 wherein the photographic coupler is a pyrazolone, pyrazolotriazole, or pyrazolobenzimidazole that forms magenta dyes.

37. The polymeric particle of claim 24 wherein the photographic coupler is an open chain ketomethylene compound that forms yellow dyes.

38. The polymeric particle of claim 24 wherein the high boiling organic solvent is selected from the group of compounds consisting of alkyl phthalates, aryl phthalates, alkyl amides, phosphates, phenols, alcohols, sulfoxides, esters, hydrocarbons, alkyl halides, and epoxides.

39. The polymeric particle of claim 24 wherein the high boiling organic solvent is selected from the group of compounds consisting of diethyl phthalate, dibutyl phthalate, dipentyl phthalate, diisoamyl phthalate, dibenzyl phthalate, dimethoxyethyl phthalate, dibutoxyethyl phthalate, tributyl trimellitate, acetyltributyl citrate, tributyl citrate, tripentyl citrate, dimethyl sebacate, dibutyl sebacate, dibutyl adipate, dibutyl azelate, 1,4-cyclohexylenedimethylene bis(2-ethylhexanoate), bis-ethylhexyl sulfoxide, triphenylphosphate, tricresylphosphate, trihexylphosphate, n-Hexylphenylcarbinol, 2-(p-tert, butylphenoxy)-ethanol, Acetyl n-butyl aniline, N-n-amyl succinimide, N,N-dipropyl dodecanamide, N-dodecyl pyrrolidinone, di-tert amyl phenol, phenoxy toluene, ethylhexyl hydroxy benzoate, phenylethyl benzoate, ethylhexyltoluene

sulfonamide, undecyl alcohol, oleyl alcohol, butyl methoxy benzoate, butyl phthalylbutyl glycollate, and N,N'-di-n-butyl urea.

## **Appendix II - Evidence**

None

### **Appendix III – Related Proceedings**

None